analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-535 of a wild-type HBV polymerase.

76. (New) An isolated *Hepadnavirus* mutant, comprising a mutation in the gene encoding the DNA polymerase, resulting in decreased sensitivity to a nucleoside analogue compared to a wild-type *Hepadnavirus*, wherein said mutation results in at least one amino acid addition, substitution, and/or deletion in the B domain corresponding to amino acid residues 505-529 of a wild-type HBV polymerase.

77. (New) An isolated mutant according to claim 74, wherein the nucleoside analogue is selected from the groups consisting of famciclovir, penciclovir and lamivudine.

78. (New) An isolated mutant according to claim 74 or 77, wherein the *Hepadnavirus* is woodchuck hepatitis virus.

79. (New) An isolated mutant according to claim 74 or 77, wherein the *Hepadnavirus* is duck hepatitis virus.--

REMARKS

Reconsideration is requested.

Claims 32-54 have been canceled, without prejudice.

Allowance of claim 46, and the indication that claims 42 and 43 contain allowable subject matter (as only being objected to for being based on a rejected base claim) are acknowledged, with appreciation. See, pages 1 and 6 of the Office Action of December 17, 2001 (Paper No. 21).

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Claims 55-79 have been added and, upon entry of the present amendment, will be pending. No new matter has been added.

The claims have been amended to place the claims in condition for allowance. The amendments are not believed to raise new issues requiring further search and/or consideration.

Specifically, new claim 55 above (directed to an isolated HBV mutant) is similar to claim "A" suggested by the Examiner on page 3 of Paper No. 21, but for the definition of the B domain, which the applicants have recited as amino acid residues 495-535, based, for example, on the description in the present specification at page 6, lines 9-10 (for example SEQ ID NO:24; region spanning amino acid residues 505-529); page 6, lines 13-15 (for example SEQ ID NO:25; region spanning amino acid residues 495-535); and originally-filed claim 8 (for example SEQ ID NO:44; region spanning amino acid residues 505-535). The region of SEQ ID NO:24 was previously considered, for example, as evidenced by the Examiner's proposed claim "A". The region of SEQ ID NOs: 25 and 44 were previously considered, for example, as a part of now-canceled claims 33 and 34. See also, the Examiner's proposed Claims "B" and "C", respectively (pages 3 and 4 of Paper No. 21).

New claim 56 (directed to an isolated HBV mutant) is similar to new claim 55 with the region defined by amino acid residues 505-535 (for example SEQ ID NO:44; originally-filed claim 8).

New claim 57 (directed to an isolated HBV mutant) is similar to new claim 55 with the region defined by amino acid residues 505-529 (page 6, lines 9-10 (for example SEQ ID NO:24)).

New independent claim 58 (directed to an isolated HBV mutant) corresponds to now-canceled dependent claim 43, which the Examiner indicated as being objected-to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. New independent claim 58 is submitted to be in condition for allowance and an indication of the same is requested in the Examiner's next communication.

New dependent claim 59 (directed to an isolated HBV mutant), which is dependent on new claims 55 and 58, includes subject matter previously considered, for example, in now-canceled claim 36.

New dependent claims 60 and 61 (directed to isolated HBV mutants), which are dependent on new claims 55, 58 and 59, include subject matter previously considered in now-canceled claim 35, as B domain amino acids.

New independent claim 62 (directed to an isolated HBV mutant) similarly includes subject matter previously considered in now-canceled claim 35, as B domain amino acids.

New independent claim 63 (directed to an isolated HBV mutant) similarly includes subject matter previously considered in now-canceled claim 35, as B domain amino acids and a C domain mutation (i.e., Ser 559Thr) not found in the cited art, and subject matter previously considered, for example, in now-canceled claim 40.

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New dependent claim 64 (directed to an isolated HBV mutant), which is dependent on new claims 62 and 63, includes subject matter previously considered, for example, in now-canceled claim 36.

New independent claim 65 (directed to a method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir), includes subject matter previously considered, for example, in now-canceled claim 44, with the recitation of screening for a mutation in a nucleotide sequence encoding the B domain of HBV polymerase corresponding to amino acid residues 495-535, as recited in, for example, new independent claim 55, as discussed above.

New independent claim 66 (directed to a method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir) is similar to new claim 64, but for the recitation of the B region found in new independent claim 56.

New independent claim 67 (directed to a method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir) is similar to new claim 64, but for the recitation of the B region found in new independent claim 57.

New independent claim 68 (directed to a method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of lamivudine, penciclovir and famciclovir) includes subject matter previous

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considered in, for example, now-canceled claim 45, and has been drafted based on the Examiner's helpful comments found on pages 5-6 of Paper No. 21.

New independent claim 69 (directed to a method for determining the potential for an HBV to exhibit, relative to an isolated wild-type HBV, reduced sensitivity to at least one of penciclovir and famciclovir) includes subject matter previous considered in, for example, now-canceled claim 45, and has been drafted based on the Examiner's helpful comments found on pages 5-6 of Paper No. 21, and not described or suggested in the art of record yet first discovered by the applicants.

New dependent method claim 70 includes subject matter previously considered in, for example, now-canceled claim 47.

New dependent method claim 71 includes subject matter previously considered in, for example, now-canceled claim 48.

New dependent method claim 72 includes subject matter previously considered in, for example, now-canceled claim 49.

New independent method claim 73, is similar to now-canceled claim 54, and finds support, for example, the HBV DNA polymerase assay described in Example 4 (spanning pages 20-21 of the specification), which the applicants believe will be recognized as being useful to screen for potential new drugs. Basis for a drug screening assay is also believed to be provided by, for example, the paragraph spanning pages 2-3 of the specification. No new matter has been added.

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New claims 74-77 (to mutants) are similar to new claims 55-57 and 63, respectively, and recite subject matter previously considered in now-canceled claims 50 and 51.

New dependent claims 78 and 79 (to mutants) recite subject matter previously considered, for example, in now-canceled claims 52 and 53, respectively.

Entry of the above amendments is requested.

The Section 112, second paragraph rejection of claims 32-34, 37-39, 41, 44, 45 and 47-53, is moot in view of the above. As noted above, the claims have been rewritten based on the Examiner's helpful suggestions in the suggested or proposed claims "A", "B" and "C" on pages 3-4 of Paper No. 21. The B domain has been defined in the above in terms of the region of amino acids, as described in the specification. More specifically, the subject matter of claims 33-34 have been rewritten so as to obviate the Examiner's rejection. The specific objected-to recitations of now-canceled claims 37-38 have not been repeated. The subject matter of now-canceled claim 41 has been recited to provide clear antecedent basis. The method of claim 45 has been rewritten to provide an interpretation step, as suggested by the Examiner. The claims are submitted to be definite.

The Section 112, first paragraph rejection of claim 54 is moot in view of the above. Support for new claim 73 is noted above. No new matter has been added.

The Section 102 rejection of claims 32-41, 50 and 51, over Ling (1996) is moot in view of the above.

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The rejected claims are all directed to mutants, as opposed to the previously claimed methods. The amended claims are submitted to be patentable over Ling. Consideration of the following in this regard is requested.

Ling discloses, at best, the following mutations in the DNA polymerase: L526M + M550V (patient 1) and F512L + M550I (patient 2). The 512 and 526 mutation reside in the B domain, while the 550 mutation resides in the C domain of the DNA polymerase. Ling may, at best, may be considered to have suggested that the resistance to lamivudine would be due to the 550 mutation in the C domain. The Examiner appears to appreciate this in admitting that "Ling does not state that these [i.e., Phe512Leu or Leu526Met, B domain mutations] are responsible for the resistance ..." See, page 4 of Paper No. 21.

The new mutant claims are directed to mutations in the B domain, which are not decribed, or suggested by the cited art. As the applicants believe they were first to recognize however the link between mutations in the B domain and resistance to nucleoside analogues, the applicants believe they are entitled to patent claims as recited above. As noted above, claim 63 includes a C domain mutation, for which there is no description in the cited art. The claims are submitted to be patentable over Ling (1996).

The Section 103 rejection of claims 45 and 47-49 over Ling (1996) is moot in view of the above. The amended claims are submitted to be patentable over the cited art. Consideration of the following in this regard is requested.

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The rejected claims 45 and 47-49 are all directed to methods, as opposed to the previously claimed mutants. The new method claims, such as new claims 68 and 69 either have been drafted to exclude the mutations which were the basis of the Examiner's concern, or are not directed to screening for sensitivity to lamivudine which, at best, is the subject matter of Ling (1996), as noted by the Examiner on page 6 of Paper No. 21. Accordingly, the claims are submitted to be patentable over the cited art.

In view of the above, the claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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IN[redacted] UNITED STATES PATENT AND TRA[redacted]ARK OFFICE

RESPONSE UNDER RULE 116
EXPEDITED HANDLING PROCEDURES

In re Patent Application of

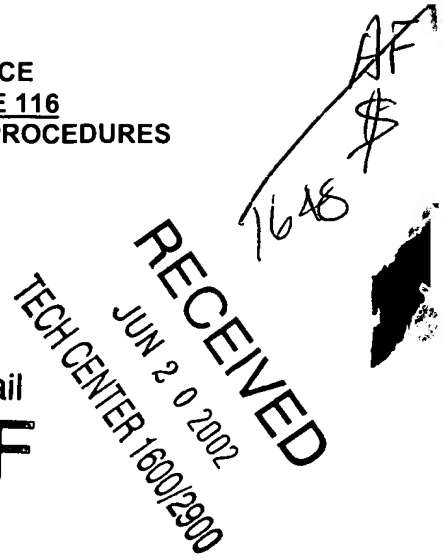
LOCARNINI et al

Serial No. 09/306,420

Filed: May 6, 1999

Title: VIRAL VARIANTS AND METHODS FOR DETECTING SAME

Atty Dkt. 2551-28
C#/M#
Group Art Unit: 1648
Examiner: Mosher, M.
Date: June 17, 2002



Corres. and Mail
BOX AF

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

Fees are attached as calculated below:

Total effective claims after amendment **37** minus highest number Previously paid for **43** (at least 20) =	0	x	$ 18.00		$	0.00
Independent claims after amendment **15** minus highest number Previously paid for **13** (at least 3) =	2	x	$ 84.00		$	168.00
If proper multiple dependent claims now added for first time, add $280.00 (ignore improper)					$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this Paper and attachment(s) ($110.00/1 month; $400.00/2 months; $920.00/3 months)					$	920.00
Terminal disclaimer enclosed, add $ 110.00					$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($740.00) ☐ Please enter the previously unentered , filed ☐ Submission attached					$	0.00
				SUBTOTAL	$	**1088.00**
Less three month extension fee ($920) paid on attached Notice of Appeal ☐ Applicant claims "small entity" status. ☐ Statement filed herewith					-$	920.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)					$	0.00
Assignment Recording Fee ($40.00)					$	0.00
Other:						**0.00**
				TOTAL FEE ENCLOSED	$	**168.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty.: B. J. Sadoff, Reg. No. 36,663

Signature: _____

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